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Time-Dependent Effects of apoE Reduction Using Antisense Oligonucleotides in a Model of β-amyloidosis

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Extensive clinical studies have established the Apolipoprotein E (*APOE*) gene on chromosome 19 as the strongest genetic risk factor for late-onset Alzheimer disease (AD). Using human *APOE* knock-in mice, it was previously demonstrated that *Apoe*-hemizygous APP/PS1 mice have significantly less amyloid plaque deposition and microglial activation compared to their homozygous littermates. Since apoE levels were lower in *Apoe* hemizygous mice for their entire life, it was not clear from a mechanistic and therapeutic perspective whether lowering apoE levels pharmacologically in adult animals would affect amyloid deposition. Here, we utilize an apoE antisense oligonucleotide (ASO) to reduce apoE expression in the adult APP/PS1-21 mice homozygous for the human ε4 allele of *APOE*. Despite achieving reduction of apoE expression by more than 50% starting at the onset of amyloid deposition, no reduction of Aβ pathology is detected when mice were assessed at four months of age. Though there was not an overall reduction in amyloid deposition, there was a clear effect of reducing apoE4 on Aβ plaque morphology. Interestingly, ASO treatment starting after birth led to a strong and significant decrease in Aβ pathology when mice were assessed at four months of age. These results suggest that apoE levels can strongly affect the initiation of Aβ pathology *in vivo* but that once Aβ plaque pathology is present, reducing apoE does not have a strong effect on further amyloid deposition. This previously unknown age-dependent effect of apoE in the early stages of Aβ plaque formation suggest the important implication that decreasing brain apoE levels would be useful for primary prevention of amyloid deposition but not for decreasing or removing amyloid plaques once they have begun depositing.